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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/394,867	09/13/99	WILLIAMS D	7037-377/IU-

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EXAMINER	
NGUYEN, D	
ART UNIT	**PAPER NUMBER**
1633	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/394,867	WILLIAMS, DAVID A.	
	Examiner	Art Unit	
	Dave Nguyen	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-93* is/are pending in the application.

4a) Of the above claim(s) *70-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-69 and 79-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

The specification, and Claims 37, 52, 57, 62, 69, 72, 76, 82, 85, 89 and 92 have been amended by the amendment filed December 27, 2000.

Applicant's election of Group I claims, *e.g.*, claims 11-69 and 79-93, in the response filed December 27, 2000 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 70-78 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Elected claims 11-69 and 79-93, to which the following grounds of rejection are applicable, are pending.

The information regarding the cross-reference to related application needs to be updated in the first paragraph of the specification. Note also that the parent applications 08/536,891 has been issued as US Pat No. 6,033,907. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32, 33, 36-47, 51-55, 57-66, 68, 69, 82, 85, 89 and 92 readable on a genus of amino acid sequences sufficiently similar to SEQ ID NO: 1 or SEQ ID NO: 2, and of amino acid sequences that must exhibit a binding activity as claimed, are rejected under 35 U.S.C. 112, first paragraph, as containing subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification and the state of the prior art only describe and provide sufficient description of SEQ ID NOS 1 and 2, functionally active fibronectin and fibronectin fragments that retain the claimed biological function, *e.g.*, the binding activity of the CS-1 domain of fibronectin ad of the heparin-II binding domain of fibronectin.

Applicant's disclosure of one species of functionally active fibronectin does not provide sufficient description of the specific structures of a representative number of unspecified protein sequences other than functionally active fibronectin peptides that would support applicant's possession of the genus of amino acid sequences which must possess the claimed biological activities. In other words, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims, *e.g.* genus of similar amino acid sequences and/or unspecified amino acid sequences with the required properties as recited in the claim, requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays identifying the "agents"; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of therapeutic nucleic acid reagents.

It is not sufficient to support the present claimed invention by disclosing simply functionally active fibronectin because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any and/or all other amino acid sequences as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming all amino acid sequences that must possess the biological property as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it

has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of "amino acid sequences" and/or "similar amino acid sequences" as claimed, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 32, 33, 36-47, 51-55, 57-66, 68, 69, 82, 85, 89 and 92 readable on a genus of amino acid sequences sufficiently similar to SEQ ID NO: 1 or SEQ ID NO: 2, and of amino acid sequences that must exhibit the binding activities as claimed are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to fibronectin or fibronectin fragments that exhibit the binding activities as claimed.

The specification does not reasonably provide enablement for the presently pending claims encompassing any and/or all immobilized materials containing unspecified ligands, and any and/or all "similar amino acid sequences" as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically and with respect to the claims, since the claimed invention is not supported by a sufficient written description, particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended.

In addition, the application does not provide sufficient guidance and/or factual evidence to enable one skilled in the art to practice the Invention directed to a method for increasing the frequency of transduction of all viable mammalian cells by a replication-defective retrovirus vector by using an effective immobilized amount of material other than active fibronectin fragments which encode Heparin II binding domains, nor is it apparent how one skilled in the art reasonably extrapolates from the disclosure including the exemplified *in vitro* data to the transduction methods as claimed, wherein an increase of retroviral transductions is affected by the presence of an unspecified materials, ligands, and/or polypeptides. Furthermore, it is not apparent how one skilled in the art determines without undue experimentation on the basis of applicant's disclosure as to which polypeptides other than active fibronectin polypeptides, e.*g.*, Heparin II binding domain and VLA-4 binding domain of fibronectin, increase the transduction of a retroviral vector into any viable mammalian cells including human pluripotent stem cells. Note also that Moritz *et al.* (J. Clin. Invest, 1994) teach that the underlying biochemical and molecular mechanism of fibronectin which affects the transduction efficiency of retroviral vectors into hematopoietic stem cells is not known. In addition, the application and claims contemplate that amino acid sequences similar to SEQ ID NO: 1 (encoding a Heparin II binding domain of fibronectin) and any amino acid sequence derived or obtained from collagen or fibroblast growth factors are also effective to increase transduction of retroviral vectors into any target cell. However, it is not apparent as to how one skilled in the art identifies and/or determines, without any undue experimentation, as to which "similar amino acid sequences" is effective for binding to a retroviral vector and affects a transduction efficiency of a retroviral viral vector into any viable mammalian

cell. The problem of predicting protein structure from mere sequence data of a single amino acid or nucleic acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects of any nucleic acid sequence and finally what changes can be tolerated with respect thereto is complex and do not invariably follow empirical rules. Unpredictability is keyed on the fact that simple analysis of primary, secondary, tertiary, and quaternary structure of a polypeptide is not well correlated with the ability of the encoded DNA product to its functional activity because the relationship between the amino acid sequence of a polypeptide and its tertiary and/or quaternary structure is not well understood and is not invariably predictable (see Ngo *et al.*, in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz *et al.*, (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). Thus, one skilled in the art would have to exercise an undue experimentation to employ any polypeptides or ligands other than fibronectin for the purpose of enhancing retrovirus transduction in the a cell culture of viable hematopoietic stem cells.

For the reasons discussed above, it requires undue experimentation to practice the full scope of claimed invention as claimed, particularly given the breadth of the claims, the amount of undue experimentation necessary because of the absence of guidance and the lack of reasonable correlation between the data obtained from the working examples to the subject matter being sought in the claims, and the unpredictable nature of the art.

Claims 24, 25, 32-37, 42, 44-51, 52-56, 61-6 and 84-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, is only enabling for:

1/ An improved method of cellular grafting, comprising the steps of:

obtaining viable hematopoietic cells from an murine donor;

infecting the viable hematopoietic cells with a replication-defective recombinant retrovirus vector containing exogenous DNA to produce transduced viable hematopoietic cells, the infecting being in the presence of an immobilized amount of fibronectin and/or a fragment thereof effective to increase the efficiency of cellular transduction by the retrovirus vector; and

introducing the transduced viable hematopoietic cells into an animal recipient as a cellular graft; does not reasonably provide enablement for any other claimed embodiment wherein a therapeutically relevant effect as a result of the grafting is contemplated; and

2/ A method for increasing the frequency of transduction of hematopoietic cells *in vitro* by a retrovirus vector, comprising

infecting the viable hematopoietic cells with a replication-defective recombinant retrovirus vector containing exogenous DNA to produce transduced viable hematopoietic cells, the infecting being in the presence of an immobilized amount of fibronectin and/or a fragment thereof effective to increase the efficiency of cellular transduction by the retrovirus vector.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification demonstrates the increased frequency of transduction of NIH/ 3T3 and clonogenic bone marrow cells using a medium containing active fibronectin fragments (active for binding to both target cells and retrovirus vectors, Example 15). Examples 1-11, and 13-14 demonstrates the efficiency of transduction of various types of viable cells, *e.g.*, hematopoietic stem cells, c-KIT+ cells, BFU-E cells, progenitor cells, and cord blood cells, by a replication-defective retrovirus in a medium containing fibronectin fragments and polybrene.

Since the application indicates that "the invention provides a method of somatic gene therapy which involves *in vitro* cellular therapy and subsequent transplantation of target cells into a host, also known as "engraftment" of the host with the transduced target cells. Thus, the only intended use of the cellular grafting methods in the absence of the stated positive effect cited in the claims is to have a therapeutically relevant effect in any and/or all animals. However, the specification fails to disclose as to what are the metes and bounds of a stated positive effect resulted from *in vivo* cellular grafting methods as claimed. No details are given for administration of the cells, such as numbers of cells needed for a particular injury or disease, or the route of administration for each application. The specification fails to provide guidance to the

artisan on these essential aspects of the invention. When treating different types of injury using the grafting methods, can the cells be infused intravenously and be expected to have sufficient gene expression to correct a defect at any target site? Are the dosage of transduced viable cells, pluripotent stem cells, for e.g. treatment of protein deficiency different from treatment for improving resistance to chemotherapy? What number of cells is sufficient? The answer to each of these questions is essential to the successful use of the invention, however the specification gives no guidance as to the essential factors so as to enable one skilled in the art to practice the full scope of the claimed invention as claimed. Furthermore, the state of the art exemplified by Moritz *et al.* indicates that *ex vivo* gene therapy using genetically modified cell for engraftment into any an animals remain unpredictable. Note the Moritz *et al.* reference (J. Clin. Invest. 1994, 93:1451-1457) indicating that "although gene transfer and long term gene expression in repopulating stem cells have been achieved in murine models by a number of investigators, *in vivo* experiments in larger animals such as dogs and primates have met with limited success, largely because of the low efficiency of infection of primitive hematopoietic stem cells". Thus, in absence of any *in vivo* data regarding the grafting methods in any and/or all animals other than a murine model, it is not apparent how one skilled in the art determines the appropriate combination of transfection method, level of expression, cell numbers and method of administration for each possible gene, so as to have a therapeutic effect in any and/or all animals, without undue experimentation.

More specifically as to the state of the art of *ex vivo* gene therapy of employing any genetically modified hematopoietic cell expressing a transgene coding for an enzyme, e.g., adenosine deaminase, Onodera *et al.*, Acta Haematologica, 101, 2, pp. 89-96, 1999, indicates that even in 1999, the retroviral-mediated gene transfer to hematopoietic stems was insufficient for achievement of any therapeutically relevant effect (abstract). Kohn , Current Opinion in Pedatrics, 7, 56-63, 1995, indicates that the efficiency of gene transfer into stem cells was much lower when similar protocols were assessed in large mammals and in human gene therapy trials, suggesting that there are species-specific differences in the susceptibility of stem cells to retrovirus infection" (p. 58, column 1). Kohn further teaches that effective gene therapy for

hematologic disorders remains unpredictable, and that a detection of circulating vector sequences in the blood *in vivo* after a transplantation of hematopoietic stem cells containing gene therapy vectors is not equivalent to a therapeutic effect (page 59, columns 1 and 2). There are no working examples in the specification which indicates the efficiency of transduction in pluripotent HSCs of any mammal including humans wherein a therapeutic effect is generated. With respect to a type of stem cells used in the claimed method, one skilled in the art would require its isolation, and the establishment of its long term stem cells. In view of the difficulty of isolating the entire range of stem cells, such as sweat gland, mucous stem cells, and human pluripotent hematopoietic stem cells, and further in the absence of any guidance with respect to a produced therapeutic effect due a number of obstacles in view of the reasons set forth in the stated rejection, it would require undue experimentation for one skilled in the art to practice the claimed invention as claimed without undue experimentation, particularly on the basis of applicant's disclosure and the doubts expressed in the art of record. More specifically as to claims encompassing gene therapy methods of employing autologous, allogeneic and xenogeneic transplantation of nearly any genetically modified cell from any mammal to any other mammal to have a therapeutic effect, transplanted cells from any subject to any other subject may not be truly syngeneic with their host mammal. Any such transplantation into immunocompetent hosts would result in a strong rejection response which would ultimately destroy the host. Thus, the specification gives no guidance as to how to control such immune responses in any mammal if such transplantation is employed in the claimed methods, nor is it apparent what diseases or disorder are effected by the transplanted cells expressing a therapeutic gene. In fact, the state of the art exemplified by Riddell *et al.* (Nature Medicine, Vol. 2, 2:216-223, 1996) indicates that one unexpected insight from *ex vivo* gene therapy against HIV infected cells in a immuno-competent host was the ability of HIV-infected patients to induce strong primary T-cell immune responses to foreign antigens expressed by transferred autologous cytotoxic CD8+ T cells (p. 221, column 1), and that the rejection of genetically modified cells by immunocompromised hosts suggests that strategies to render gene-modified cells less susceptible to host immune surveillance will be required for successful gene therapy of immuno-competent

hosts (abstract, page 221, column 1).

Even if some of the genetically modified immune cells escape from the immune response in a survived host after systemic administration, it is further not apparent to one skilled in the art as to how the genetically modified immune cells traverse though barriers such as peripheral vein and endothelial wall to reach target diseased cells, e.*g.*, cancerous, virally infected cells, so as to generate any and/or all therapeutic effects as contemplated by applicants. Thus, it is not apparent how the murine model wherein hematopoietic stems expressing ADA were grafted as evidenced in the prior art at the time the invention was made is reasonably extrapolated to any and/or all therapeutically relevant effects generated in any and/or all diseased animals other than mice by using the claimed materials and/or method steps, particularly in view of the reasons set forth above. Note that while the improvement claims indicates an improvement of existing cellular grafting methods of employing genetically modified hematopoietic stem cells in any and/or animal, cellular grafting methods of employing genetically modified hematopoietic stem cells in any and/or animal that exists in the prior art of record and the improvement method as claimed so as to have a therapeutic effect still remain unpredictable at the time the invention was made, particularly given the reasons set forth above and the doubts expressed in the art of record.

In view of the lack of guidance regarding the breadth of the claims, state of the art and the unpredictability of the art, as set forth by the evidence presented above, undue experimentation would be required by one of ordinary skill to practice the full scope of the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23, 33, 37, 41, 49, 52, 55, 57, 60 62, 65, 82, 85, 89 and 92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37, 52, 57, 62, 82, 85, 89 and 92 are indefinite in the recitation of "sufficiently similar" because the term is relative in meanings and does not contain a reference point for determining applicant's intended scope of the claims. In addition, the "primitive" is indefinite because it is not apparent as to what is exactly the metes and bounds of the "primitive". What are exactly the types of hematopoietic cells that fall within the scope of "primitive hematopoietic cells"?

Claims 23, 33, 41, 49, 55, 60 and 65 are indefinite in the recitation of "low density" because "low" is relative in meanings and does not identify applicant's intended scope of the claims.

Claim 47 is objected because "rcombinant" should be typed as – recombinant –.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. ' 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. ' 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 11-13, 23, 26, 28, 29, 31-33, 36-41, 43, 52, 57, 58, 68, 69, 79-83, 87-89, 91 and 92 are rejected under 35 U.S.C. 102(b) as being anticipated by either David A. Williams *et al.* (Blood Cells, 20, pp. 504-516, 1994, IDS), or Moritz *et al.*, J. Clin. Invest. 1994, 93:1451-1457.

Williams and Moritz teach a method of obtaining retrovirus transduced blood stem cells comprising infecting the cells with a retrovirus vector expressing a transgene on FN 30/35 coated dishes so as to enhance the infection efficiency (entire document, especially p. 510, Fig. 6, and p. 511). With regard to the use of other extracellular proteins including type IV collagen, Williams on page 510 teaches the method wherein collagen IV coated plates were employed to enhance the retrovirus infection. The Williams reference as a whole clearly teaches that as long as FN 30/35 coated plates were employed for culturing the retrovirus infecting the blood cord stem cells, transfection efficiency will be generated as a result of the use of FN 30/35 during the culturing and infection process.

Absent evidence to the contrary, the processes disclosed in the references have all of the properties cited in the claims.

Claims 68, 69 and 79-83 are rejected under 35 U.S.C. 102(b) as being anticipated by Haberman (US Pat No. 5,354,686).

Haberman teaches a method for transducing T cells with a retrovirus, comprising infecting the cells with the retrovirus in the presence of a supporting material comprising any known extracellular proteins including fibronectin which comprises SEQ ID NO: 1.

Absent evidence to the contrary, the transfection method of Haberman has all of the properties cited in the claims.

Claims 11-14, 16, 23-39, 44, 45, 47-50, 52-53, 56-58, 62, 63, 67-69 and 79-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lim *et al.*, PNAS, Vol. 86, pp. 8892-8896, 1989, taken with any of David A. Williams *et al.* (Blood Cells, 20, pp. 504-516, 1994, IDS), Moritz *et al.*, J. Clin. Invest. 1994, 93:1451-1457, Williams and Patel (US Pat No. 5,686,278) and Finer (US Pat No. 6051,427), and further in view of applicant's admission over the prior art of record on pages 16 and 23 of the as-filed application.

Lim *et al.* teach a method of grafting murine stem cells enriched in hematopoietic stem cells transduced by a replication defective retroviral vector expressing a human ADA gene for long-term expression of the ADA gene in mice transplanted with the cells (entire disclosure). Culture medium containing the transfected stem cells is also disclosed in the Lim *et al.* reference.

Lim *et al.* do not teach the concept of employing functionally active fibronectin, e.*g.*, FN 30/35 which contain both the binding domains as recited in the claims, to facilitate or enhance the transduction of retrovirus vectors into the cells.

However, at the time the invention was made, Williams, Moritz, Williams and Patel, and Finer *et al.* teach a method of obtaining retrovirus transduced blood stem cells comprising infecting the cells with a supernatant containing retrovirus vectors expressing a transgene on FN 30/35 coated dishes so as to enhance the infection efficiency (entire document, especially p. 510, Fig. 6, and p. 511). With regard to the use of other extracellular proteins including type IV collagen, Williams on page 510 teaches the method wherein collagen IV coated plates were employed to enhance the retrovirus infection. The Williams, Moritz, Williams and Patel, and Finer *et al.* references as a whole clearly teach that as long as functionally active fibronectin including FN 30/35 coated plates were employed for culturing the retrovirus infecting the stem cells, transfection efficiency will be generated as a result of the use of fibronectins during the culturing and infection process.

In addition, pages 16 and 23 of the as-filed specification teaches that functionally active fibronectin fragments including H-296 and CH-296 are available in the prior art of record.

It would have been obvious for one of ordinary skill in the art to have employed any fibronectin fragments known in the prior art as long as the fragments contains the essential domains of the FN-30/35 in the grafting method and/or cultures and/or compositions of Lim *et al.* One of ordinary skill in the art would have been motivated to have employed fibronectin fragments including the FN-30/35, H-296 and CH-296 in the grafting methods and/or compositions of Lim *et al.* so as to increase the retroviral transduction into the stem cells, as taught by the Williams, Moritz, Williams and Patel, and Finer *et al.* references.

In addition, it would also have been obvious for one of ordinary skill in the art to not employ a co-cultivation step or retroviral producer cells because the Williams, Moritz, Williams and Patel, and Finer *et al.* references as a whole clearly teach that as long as functionally active fibronectin including FN 30/35 coated plates were employed for culturing a supernatant containing the retrovirus expressing a transgene and stem cells desired for retroviral transduction, transfection efficiency will be generated as a result of the use of fibronectins during the culturing and infection process.

Claims 11-23, 26-43, 52-61, 68, 69, 79-83, 87-89 and 91-93 are rejected under 35 U.S.C. 102(e) as being anticipated by, or in the alternative, under 35 U.S.C. 103(a), as being unpatentable over either Williams *et al.* (US Pat No. 5,686,278), or Finer (US Pat No. 6051,427).

Williams *et al.* and Finer *et al.* teach a method of obtaining retrovirus transduced blood stem cells including human stem cells or cord blood cells deficient in ADA comprising infecting the cells with a supernatant containing retrovirus vectors expressing a transgene, e.*g.*, ADA, on FN 30/35 coated dishes so as to enhance the infection efficiency (entire documents, especially columns 7-12 of Williams *et al.* and columns 41-44 of Finer *et al.*). The Williams *et al.* and Finer *et al.* references as a whole clearly teach that as long as functionally active fibronectin including FN 30/35 coated plates were employed for culturing the retrovirus infecting the stem cells, transfection efficiency will be generated as a result of the use of fibronectins during the culturing and infection process.

Absent evidence to the contrary, the methods, cultures and compositions of the references have all

of the properties cited in the claims, or at least, in the alternative, would have been obvious over the methods and compositions as claimed.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-23, 26-43, 52-61, 68, 69, 79-83, 87-89 and 91-93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,686,278 or claims 1-14 of US Pat No. 6.033.907.

Although the conflicting claims are not identical, they are not patentably distinct from each other because all three sets of claims are readable on

A method for obtaining a transduced population of viable mammalian cells by a retrovirus expressing ADA, a composition containing the transduced populations, and a method of enhancing the transduction of retrovirus vectors into hematopoietic cells, wherein all of the methods and compositions require the presence of substantially pure fibronectin, substantially pure fibronectin fragments, or a mixture thereof, so as to increase the frequency of transduction of the hematopoietic cells by the retrovirus vector.

No claims are allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Kimberly Davis, whose telephone number is **(703) 305-3015**.

Any inquiry concerning this communication or earlier communications from the examiner should be

directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Clark*, may be reached at **(703) 305-4051.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen

Patent Examiner

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